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Phase 2 Trial of Cixutumumab in Children, Adolescents and Young Adults with Refractory Solid Tumors: A Report from the Children's Oncology Group

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Abstract

Purpose—This phase 2 study was designed to assess the efficacy of single agent cixutumumab (IMC-A12) and gain further information about associated toxicities and pharmacodynamics in children, adolescents, and young adults with recurrent or refractory solid tumors.

Patients and Methods—Patients with relapsed or refractory solid tumors were treated with 9 mg/kg of cixutumumab as a 1-hour IV infusion once weekly. Strata included: osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma (evaluable disease), neuroblastoma (measurable disease), Wilms tumor, adrenocortical carcinoma, synovial sarcoma, hepatoblastoma, and retinoblastoma. Correlative studies in consenting patients included an assessment of c-peptide, IGFBP-3, IGF-1, IGF-2, hGH, and insulin in consenting patients.

Results—One hundred and sixteen patients with 114 eligible having a median age of 12 years (range, 2-30) were enrolled. Five patients achieved a partial response: 4/20 with neuroblastoma (evaluable only) and 1/20 with rhabdomyosarcoma. Fourteen patients had stable disease for a

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median of 10 cycles. Hematologic and non-hematologic toxicities were generally mild and infrequent. Serum IGF-1 and IGFBP-3 increased in response to therapy with cixutumumab.

Conclusion—Cixutumumab is well tolerated in children with refractory solid tumors. Limited objective single-agent activity of cixutumumab was observed; however, prolonged stable disease was observed in 15% of patients. Ongoing studies are evaluating the toxicity and benefit of cixutumumab in combination with other agents that inhibit the IGF pathway.

Keywords

Investigational Agents; Insulin-like Growth Factor-I Receptor; Pediatric Cancer; Monoclonal Antibody

Introduction

The insulin-like growth factor-I receptor (IGF-IR) plays a role in the initiation and progression of a variety of cancers, including many malignancies of childhood and young adults.[1-9] Preclinical data suggest that inhibition of the IGF-IR may constitute an important therapeutic target in a variety of pediatric solid tumors, including rhabdomyosarcoma, neuroblastoma and Wilms tumor.[10-15]

Cixutumumab (IMC-A12; ImClone Systems, Inc., Branchburg, NJ), a human IgG1/λ monoclonal antibody (mAb) against the IGF-IR, binds to the IGF-IR with high affinity, decreases cell surface IGF-IR expression, and blocks interactions with IGF-I and IGF-II ligands.[16-18] In preclinical cancer models, cixutumumab has single-agent activity and potentiates the effect of cytotoxic therapy in vitro and in vivo.[19-22] When evaluated by the Pediatric Preclinical Testing Program, cixutumumab demonstrated single-agent activity in osteosarcoma, Ewing sarcoma (ES), neuroblastoma, glioblastoma, and rhabdomyosarcoma models.[23]

In a single-agent phase 1 study in adults, cixutumumab was well tolerated at doses from 3 to 15 mg/kg weekly, and a maximum tolerated dose (MTD) was not defined.[24,25] Based on pharmacokinetic data, the recommended phase 2 dose in adults is 6 mg/kg when given weekly.[24]

A phase 1 study of cixutumumab (ADVL0712) conducted by the Children's Oncology Group (COG) Phase 1 Consortium in children and adolescents patients with refractory non-CNS solid tumors included a phase 2 expansion cohort for relapsed/refractory Ewing sarcoma (ES). The recommended phase 2 dose defined in this trial, 9 mg/kg, was higher than that in adult phase 2 trials, which reflects a more rapid clearance in children than adults.[26] We now report the results of the COG phase 2 study of cixutumumab in children, adolescents and young adults with relapsed/refractory non-CNS solid tumors.

Patients and Methods

Patient Population

Patients between 1 and 31 years of age with measurable disease and relapsed refractory solid tumors including osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, synovial sarcoma, Wilms tumor, hepatoblastoma, and adrenocortical carcinoma were eligible for trial. Patients with neuroblastoma and MIBG only evaluable disease were also eligible. Other eligibility criteria included standard organ function and performance status requirements as well as the absence diabetes mellitus and known metastatic disease to the central nervous system.[26] Patients receiving other anti-cancer agents, insulin, or growth hormone were not eligible.

The trial was approved by individual institutional review boards (IRBs) of participating sites, as well as the National Cancer Institute Pediatric Central IRB. All patients or their parent/legal guardian signed a document of informed consent; assent was obtained as appropriate prior to enrollment.

Drug Administration

Cixutumumab was supplied in 250-mg (5 mg/ml) or 500-mg (10 mg/ml) single use vials by the NCI (Bethesda, MD). It was administered as a 1-hour intravenous infusion (at a rate ≤ 25 mg/min) through a 0.2 or 0.22 μm protein-sparing filter once weekly in continuous 28 day cycles. All patients received the recommended phase 2 dose of 9 mg/kg.

Cycles were repeated without interruption if the patient did not have progressive disease and had recovered from the prior cycle with an ANC of ≥ 750/μl, platelet count ≥ 50,000/μl, and other laboratory parameters meeting eligibility criteria. Patients who experienced hyperglycemia could continue on protocol therapy if they were asymptomatic and their serum glucose was maintained at < 250 mg/dL (≤ grade 2) with or without the use of insulin or an oral hyperglycemic agent. Patients could remain on protocol therapy with one dose reduction to 6 mg/kg, in the event of reversible doselimiting toxicity (DLT).

Hematological dose limiting toxicities were defined as any grade 4 neutropenia or thrombocytopenia that did not resolve (ANC ≥ 750/μl; platelets ≥ 50,000/μl for all strata except patients with neuroblastoma: ANC ≥ 250/μl; platelets ≥ 25,000/μl) within 7 days of the next scheduled dose of cixutumumab. Non-hematological dose limiting toxicities were defined as any grade 4 non-hematological event; any grade 3 event (excluding nausea/vomiting controlled with anti-emetics; AST/ALT elevation that returned to eligibility levels within 7 days; fever; infection; hypophosphatemia, hypokalemia, hypocalcemia and/or hypomagnesimia that responded to oral supplementation); and grade 2 non-hematological toxicities persisting for ≥ 7 days.

Study Design

A two-stage design was used to evaluate cixutumumab in five target disease strata: osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma with measurable disease detected and neuroblastoma with MIBG-positive evaluable disease only.

Eligible patients with relapsed or recurrent Wilms tumor, synovial sarcoma, hepatoblastoma or adrenocortical carcinoma were also enrolled and the two stage design applied if sufficient patients were enrolled to the respective stratum. The study was designed to end enrollment to all strata after evaluation of the five primary target disease strata was complete. The results for the Ewing sarcoma stratum were presented previously.[26]

At the first stage for each stratum, 10 patients were enrolled. If no patient experienced an objective response, cixutumumab was considered inactive in that stratum, and enrollment to that stratum was terminated. If >1 patient(s) achieved a partial response or complete response, 10 additional patients would be enrolled to that stratum. Cixutumumab would be considered active if ≥ 3 of 20 patients in an expanded stratum experienced a partial or complete response. With this design, cixutumumab would be identified as inactive if the true response rate was 5% with a probability of 0.93, and would be identified as active if the true response rate was 25%with a probability of 88%. The point estimate of the response rate was calculated as the maximum likelihood estimate. Confidence intervals for the response rates were calculated using the method of Jung and Kim.[27]

Any eligible patient who received at least one dose of cixutumumab was considered evaluable for response provided: (1) the patient demonstrated progressive disease or died while on protocol therapy; or (2) the patient was observed on protocol therapy for at least one cycle and the tumor was not removed surgically prior to the time a complete or partial response was confirmed; or (3) the patient demonstrated a complete or partial response as confirmed by central review of radiographic images. All other patients were considered non-responders. The evaluation period for determination of the overall best response was six treatment cycles.

Toxicity evaluation

Each cycle in which cixutumumab was administered to an eligible patient was considered in the analysis of toxicity. The treating physician assigned an attribution for each CTC-gradable adverse event as unrelated, unlikely, possibly, probably, or definitely related to cixutumumab. The study originally used CTCAE v.3.0 but was amended to incorporate CTCAE v. 4.0 and toxicities are reported using the new criteria. The relative frequency of each adverse event considered possibly, probably, or likely related to cixutumumab was estimated as the proportion of all toxicity-evaluable cycles in which such toxicity was observed.

Patient Evaluation

History, performance status, physical examination and serum electrolytes were obtained at baseline, weekly throughout cycle 1, and before each subsequent cycle. Complete blood counts and serum/urine glucose were obtained weekly throughout treatment. Disease evaluations for patients enrolled with measurable disease were performed after cycle 1 and after each subsequent odd-numbered cycle using Response Evaluation Criteria in Solid Tumor (RECIST).[28] For patients enrolled with MIBG positive evaluable disease only, response was assessed using the Curie scale.[29]

Central review of responses was performed to confirm responses and for stable disease greater then 6 months.

Pharmacodynamic Studies

Serum samples were obtained on days 1, 8 and at the end of cycle 1. Serum IGF-I, hGH and IGFBP-3 concentrations were measured using commercial ELISA kits from Diagnostic Systems Laboratories (Webster, TX). Insulin and c-peptide were measured and analyzed using commercial assays by Immunolite, Siemens Healthcare Diagnositics, USA. Serum samples for IGF-II were analyzed by ELISA from Biovendor, (Candler, NC). Results are expressed as individual patient values at each time point analyzed.

Results

Patient Characteristics—This study (study code: ADVL0821; ClinicalTrials.gov identifier: NCT00831844) was opened in January 2009 and closed in March 2012. Data as of September 2012 were used in the analyses. One hundred sixteen (116) patients were enrolled. Fourteen (14) patients with Ewing sarcoma are excluded from this report as these patients have been previously reported.[26] Two the remaining 102 subjects were ineligible: one had a diagnosis not eligible for the study and one had baseline scans outside the maximum allotted pre-treatment window of 14 days. There were also two patients with measureable disease (osteosarcoma (n=1) and Wilms n=1)) from the phase 1 trial who were included in this analytic cohort in accordance with the prospective protocol design. These two subjects were enrolled at the recommended phase 2 dose on ADVL0712, the phase 1 trial of cixutumumab. The characteristics of all eligible patients in the analytic cohort are described in Table 1. Two eligible patients (osteosarcoma and synovial sarcoma) were considered inevaluable for response assessment due to rapid progressive disease prior to administration of study drug; neither patient received cixutumumab on study and both were replaced to ensure 10 evaluable patients per cohort. At the time of the analysis one patient remained on protocol therapy after completing 24 cycles of cixutumumab.

Antitumor Activity

Five partial responses were observed: four in patients in the neuroblastoma (evaluable only) stratum and one in the rhabdomyosarcoma stratum. The median number of cycles for patients with a PR was 11 (range 9-24). Two patients neuroblastoma completed 24 months of therapy (the maximum allowable duration) and the others completed 9 and 11 cycles of therapy prior to disease progression. The patient with rhabdomyosarcoma completed 10 cycles of therapy.

No objective responses were observed in the 10 evaluable patients enrolled in each of the remaining two primary disease strata (osteosarcoma and neuroblastoma with measurable disease). Likewise, no objective responses were observed in the nontarget strata (Wilms tumor, hepatoblastoma, adrenocortical carcinaoma, synovial sarcoma), which each enrolled 10 evaluable patients.

The median number of treatment cycles for all response evaluable patients was 1 (range 1–24). Nineteen patients (19) were evaluated as SD (14 patients) or PR (5 patients). Stable disease occurred across a spectrum of solid tumors, including one patient each with adrenocortical carcinoma (7 cycles), osteosarcoma (5 cycles) and Wilms tumor (5 cycles); two patients with synovial sarcoma (5 and 7 cycles); three patients with rhabdomyosarcoma (5, 7, and 22 cycles, four patients with neuroblastoma (measurable disease) (10, 11, 13 and 20 cycles), and two patients with neuroblastoma (evaluable only) (11, and 19 cycles). These patients with SD received a median of 10 (range 5–22) cycles of therapy.

According to the protocol design, cixutumumab is considered of sufficient efficacy for further development only in the neuroblastoma (evaluable only) stratum. The point estimate of the response rate was 20% with associated 95% confidence interval 8.8%-47%.

Toxicity

The 100 patients who were evaluable for toxicity received 364 treatment cycles. Grade 2 and higher toxicities are shown Table 2. The only grade 4 toxicities were hematological (anemia [n=1], neutropenia [n=2], lymphopenia [n=1], low platelet count [n=2]), Mild hyperglycemia (Grade 2), which did not require treatment, was observed in 9 patients. Five patients were removed from protocol therapy due to dose limiting toxicities, include two grade 3 elevation in hepatic enzymes (one patient with hepatoblastoma at the end of cycle 1 and the other during cycle 10 in a patient with neuroblastoma); two grade 3 allergic reactions to the first dose of cixutumumab; and one grade 4 thrombocytopenia at the end of cycle 1 in a patient with neuroblastoma. No other dose modifications due to toxicity were required.

Pharmacodynamics

A total of 17 patients consented and had sufficient samples to assess serum biomarkers (osteosarcoma 2; rhabdomyosarcoma 3; neuroblastoma MIBG evaluable only 2; adrenocortical carcinoma 3; synovial sarcoma 4; hepatoblastoma 3). A marked increase in mean serum IGF-I and a moderate increase in serum IGFBP-3 and c-peptide relative to baseline was observed in all patients evaluated following one dose of cixutumumab. Serum IGF-II, insulin, and growth hormone concentrations did not appear to consistently change from baseline.

Discussion

Cixutumumab given weekly IV at the recommended pediatric phase 2 dose of 9 mg/kg was well tolerated in this multi-strata phase 2 study. Similar to previously published data for other IGF-R antibody therapies and for the Ewing sarcoma cohort using cixutumumab the response rate in this study was low in all strata studied except for patients with neuroblastoma who had evaluable only disease.[26,30,31] In this select cohort the response rate was 20% (4/20 PR), however, prolonged stable disease or partial response was achieved over 5 or greater cycles in 19/80 patients with a variety of diseases.

To date, serum biomarkers of response to IGF-IR inhibition have not been able to predict or correlate with anti-tumor response. In the pediatric phase I trial of cixutumumab the tumor

expression of IGF-IR by immunohistochemistry did not correlate with response, however, as confirmed in this larger pediatric study there was uniform serum increases in IGF-1 and IGFBP-3 after one dose of therapy.[26] This suggests that more robust biologic predictors of anti-tumor response are needed to further develop this class of agents and maximize clinical benefit.

Several studies have suggested that IGFR inhibition alone is insufficient to achieve and/or sustain an anti-tumor response due to increased reliance of the tumor cell on other survival mechanisms.[32,33,34] Thus combination strategies with other targeted agents are attractive to overcome these potential escape mechanisms.

Trials combining cixutumumab with chemotherapy and other novel agents are underway. COG is conducting a phase 1 study of cixutumumab with temsirolimus in solid tumors and a pilot study combining cixutumumab with multi-agent chemotherapy for metastatic rhabdomyosarcoma. In addition, there are several ongoing phase 1 and 2 combination studies of IGFR inhibitors in adults with a variety of solid tumors.

In summary, cixutumumab is well tolerated in children, adolescents and young adults as a single-agent at 9 mg/kg. Patients with neuroblastoma with only MIBG evaluable disease achieved the targeted 20% partial response rate in the first 6 months of therapy. Prolonged stable disease was observed in 15% of patients with a variety of solid tumor types. Ongoing studies are evaluating the toxicity and benefit of cixutumumab in combination with other agents that inhibit the IGF pathway..

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Table 1

Characteristics for eligible patients (n=102)

Characteristic	Number of Patients
Age (years)	
Median	12 yrs
Range	2-30 yrs
Sex	
Male	52
Female	50
Race	
White	68
African American	15
Native American	1
Asian	4
Other/Unknown	14
Diagnosis Target Strata	
Osteosarcoma	11
Rhabdomyosarcoma	20
Neuroblastoma (evaluable disease)	20
Neuroblastoma (measurable disease)	10
Non-Target Strata	
Wilms Tumor	10
Adrenocortical carcinoma	10
Hepatoblastoma	10
Synovial sarcoma	11

Table 2

Grade 2 and higher toxicities related to protocol therapy.

Toxicity Type	Maximum grade of toxicity Cycles 1-24 (total, 364 cycles)		
	Grade 2	Grade 3	Grade 4
Anemia	9	9	1
White blood cell decreased	14	2	
Lymphocyte cell decreased	14	5	1
Neutrophil count decreased	18	3	2
Platelet count decreased	18	3	2
Fatigue	14	2	
Fever (without neutropenia)	4		
Weight loss	1		
Allergic reaction	1		
Anaphylaxis		2	
Pruritus		1	
Bilirubin increased	5	1	
Cough	1	1	
Anorexia	5	2	
Dehydration	4	4	
Diarrhea	1	1	
Oral Mucositis/stomatitis	1		
Vomiting	5	4	
Infections and Infestations	1	4	
Hypoalbuminemia	8	2	
Alkaline phosphatase	1		
ALT, SGPT	8	4	
AST, SGOT	2	2	
Hyperglycemia	9		
Hypophosphatemia	7	1	
Proteinuria	3		
Hypertriglyceridemia	1		
Creatinine increase	7		
Headache	1	1	
Nausea	2	2	